S/N 09/150813 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: David J. Grainger et al. Examiner: Joseph Murphy
Serial No.: 09/150813 Group Art Unit: 1646
Filed: September 11, 1998 Docket No.: 1543.002US1
Title: COMPOUNDS AND METHODS TO INHIBIT OR AUGMENT AN INFLAMMATORY RESPONSE

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, David J. Grainger, do declare:

1. I am a named co-inventor of the present application and make this Declaration in support of the patentability of the claims of the present application as amended in the Amendment which accompanies this Declaration.

2. In the Office Action mailed March 25, 2003, the Examiner rejected claims 63-83 of the above-identified application under 35 U.S.C. § 112, first paragraph, asserting that: 1) many of the diseases encompassed by the claims do not contain an inflammatory component; 2) the nexus between chemokine induced activity and all of the diseases encompassed by the claims has not been shown; 3) the *in vitro* assays disclosed in the specification are not representative of all the listed diseases; and 4) there is no evidence in the specification that the agents can prevent a disease.

3. The claims, as amended, are generally directed to the use of chemokine peptides substantially corresponding to sequences in the C-terminal half of a chemokine, and derivatives thereof, to prevent or inhibit hematopoietic cell, e.g., leukocyte, migration or recruitment.

4. As disclosed in the specification, chemokines are associated with the inflammatory response (page 30, lines 26-29). In particular, chemokines are central regulators of leukocyte (white blood cell) recruitment or migration. Leukocyte recruitment is a central component of the inflammatory process, both in physiological host defense and in a range of prevalent disorders with an inflammatory component. As one of the major effector mechanisms of the immune system, the recruited leukocytes play a central role in host defense. They can target and destroy a wide range of invading pathogens from viruses to bacteria, and fungi to intracellular pathogens. Chemokine-induced hematopoietic cell migration and inhibition thereof, can be detected using *in vitro* assays such as the one described in the present application (page 30, lines 26-29).

5. Molecules with anti-inflammatory activity are useful for the treatment of indications where inappropriate inflammation is a contributory factor to the pathogenesis and/or clinical symptoms of the indication. The above-identified application provides a list of exemplary indications in which inflammation plays a contributory role in the pathogenesis or clinical symptoms of those indications (page 47, line 1-page 49,line 28).

6. For many of the above-described indications, the pathogenic role of leukocytes is well-known. For example, allergic rhinitis (hayfever) is an indication which is clearly due to inappropriate activation of an immune response (including leukocyte recruitment) by environmental allergens such as grass pollen. Similarly, autoimmune diseases such as rheumatoid arthritis are associated with inflammation, as activation of the immune system to attack the individual's own tissue is a key pathogenic mechanism (see Kunkel et al., J. Leuko. Biol., 59:6 (1996), a copy of which is enclosed herewith). The role of leukocyte recruitment, likely regulated at least in part by chemokines, is universally accepted as a central pathogenic mechanism in these diseases.

7. Other diseases which have an inflammatory component include atherosclerosis and osteoporosis. Although atherosclerosis is commonly seen as a disease of cholesterol metabolism, it is known that inappropriate recruitment of leukocytes is involved in the

developing atherosclerotic plaque (see U.S. Patent No. 5,770,609, a copy is included herewith). These leukocytes produce proteases which degrade the extracellular matrix and destabilize the plaque. Subsequent rupture of the leukocyte rich, unstable plaque is the proximate cause of myocardial infarction, the most serious clinical sequella of coronary heart disease (see, e.g., Watanabe et al., Int. J. Cardiol., 66:545 (1998), a copy of which is enclosed herewith, which confirms the importance of leukocyte recruitment as a contributory pathway to the clinical symptoms associated with coronary heart disease).

8. Misregulation of leukocyte recruitment is well-known to lie at the heart of osteoporosis. Bone mineral density is regulated by the balance between the mineralization activity of bone-producing cells (called osteoblasts) and mineral resorption by bone-resorbing cells (osteoclasts). Pathological low bone mineral density in osteoporosis is caused by an imbalance of osteoblast or osteoclast activity, e.g., decreased osteoblast activity or increased osteoclast activity. Osteoclast cells (bone-resorbing cells) are known to originate from the leukocyte population in blood. Recruitment of leukocytes to bone is therefore the dominant process in determining the number of osteoclasts. This, in turn, is part of the regulatory balance controlling bone mineral density. There are numerous references in the literature describing the role of leukocyte recruitment in the regulation of bone mineral density (for example, see Suda et al., Bone, 17:875 (1995), a copy of which is enclosed herewith).

9. The role of inflammation in neurodegenerative diseases such as Alzheimer's disease is also well-established (for example, see Akiyama et al., Neurobiol. Aging, 21:383 (2000), a copy is enclosed herewith). Inflammation in Alzheimer's disease is already known to be a therapeutic target: non-steroidal anti-inflammatory drugs have recently been shown to have some benefit in slowing the onset of neurodegeneration (see, for instance, McGeer et al., Brain Res. Brain Res. Rev., 21:195 (1995), a copy is attached hereto). The molecular mechanism underlying this role for leukocyte recruitment may be that leukocytes, which are responsible for clearing out the remnants of dying neuronal

cells, are inhibited by the formation of fibrillar tangles. This results in further leukocyte recruitment, and ultimately in immune-mediated damage to the remaining neurons.

10. Thus, there are numerous indications in which leukocyte recruitment or migration is important to the pathogenesis or clinical symptoms of those indications. Since chemokines are central regulators of leukocyte recruitment or migration, altering chemokine function affects leukocyte recruitment or migration dynamics and, hence, affects the progression of the disease state. Once chemokines are implicated in a disease process, agents which have hematopoietic cell inhibitory activity are likely to be useful therapeutic modalities for indications in which leukocyte recruitment or migration contributes to pathogenesis or clinical symptoms.

11. Further, administration of an agent of the invention prior to manifestation of clinical symptoms of an indication in which inappropriate inflammation is a contributory factor, can prevent or inhibit the underlying pathogenesis or clinical symptoms of the indication. See, for example, WO 00/00821, where T cell-dependent antibody responses, dermal inflammation, endotoxemia, and asthma were substantially prevented by administration of an agent of the invention. Clearly, agents of the invention may be administered prophylactically.

12. I further declare that all statements made herein of my own knowledge are true, and that all statements made on the information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 24th SEPTEMBER 2003

By David J. Grainger
David J. Grainger, Ph.D.